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Abstracts

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Department of Chemical Pharmacology

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S9-1 Overview: Role of endothelin in cardiovascular system.

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Endothelin (ET) is a potent vasoconstrictor peptide expressed in various tissues and cells. It has a variety of pharmacological functions. Three endogenous ETs, designated ET-1, ET-2 and ET-3, and two ET receptors, ETA and ETB, have been identified in mammalian tissues. In vascular beds, ET acts as both relaxing and constricting factors. When ET-1 is overproduced by endothelial cells, endogenous ET-1 acts as a vasoconstrictors in paracrine manner. However, it acts as a vasodilator at physiologically low concentrations depending on the existing conditions. In addition to controlling vascular smooth muscle tone, ET-1 also influences the tissue remodeling process following vascular wall injury. In heart tissue, ET-1 may play a role in mediating cardiac growth and function. ET acts as a differentiating factor as well as a growth factor on isolated cells.

S9-2 Endothelin antagonist: therapeutic potential for cardiovascular diseases.

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T-0201 is a new orally active nonpeptidic endothelin(ET) receptor antagonist. We studied pharmacological properties of T-0201 and the effects of T-0201 on various experimantal models of cardiovascular diseases in order to evaluate the therapeutic potential for target diseases.

In vitro, T-0201 antagonized the specific binding of [^{125}I]-ET-1 to human cloned ETA and ETB receptors with Ki values of 15pM and 41nM, respectively. *In vivo*, T-0201 (0.01-10mg/kg, i.v.) inhibited the pressor response to exogenous big ET-1(1nmol/kg, i.v.) in anesthetized rats and dogs.

In the studies in animal models of cardiovascular diseases, T-0201 showed following effects;

(1)dose-dependent hypotensive effect in stroke-prone SHR (0.1-10mg/kg, p.o.).

(2)supression of monocrotaline(MCT)-induced right ventricular hypertrophy in rats (0.03, 0.1mg/kg, p.o., bid).

(3)reduction of pulmonary arterial pressure without changing systemic blood pressure and heart rate in dehydroMCT-induced pulmonray hypertensive dogs (10μg/kg/min, i.v.).

(4)inhibition of neointima formation following balloon angioplasty of rat carotid artery (1,10mg/kg, p.o., bid).

(5)inhibition of delayed basilar artery spasm in the canine two-hemorrhage model (3mg/kg, i.v., bid).

These results indicates that T-0201 is a potent ETA-selective antagonist, and has therapeutic potential for cardiovascular diseases with vascular and cardiac remodelling.

S9-3 The vascular effects of endothelin.

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Endothelin (ET) has direct constrictor and indirect dilatator effects in blood vessels. Two types of ET receptors, ETA and ETB, were identified. Initially, it was reported that constriction is mediated by smooth muscle ETA receptor whereas dilatation is due to release of NO though the activation of endothelial ETB receptor. Recently, however, not only ETA receptor but also ETB receptor were shown to mediate constriction in smooth muscle of some arteries and veins. Also in endothelium, not only ETB but also ETA receptor seemed to mediate NO release. Furthermore, ETA receptor was suggested to be classified into ETA1 and ETA2 subtypes depending on their sensitivity to an antagonist, BQ-123. ETB receptor was also suggested to be classified into ETB1 and ETB2 subtypes depending on their sensitivity to the antagonists, IRL 1038 and RES 701-1. Smooth muscl ETA rec ptors are coupled to Ca^{2+} release, Ca^{2+} influx and increase in Ca^{2+} sensitivity of contractile elements whereas smooth muscle ETB receptors are coupl d to Ca^{2+} influx and Ca^{2+} sensitization but not to Ca^{2+} release. In contrast, endothelial ETB receptor is coupled to Ca^{2+} release and Ca^{2+} influx.

S9-4 Cardiac effects of endothelin isopeptides.

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Endothelin (ET) isopeptides, ET-1 and ET-3, elicit a positive inotropic effect (PIE) on mammalian ventricular muscle, but they show a wide range of variation among species: the rank order is: rabbit > rat, guinea pig, ferret >> dog. While in the rabbit ET-1, ET-2 and ET-3 induce a PIE with an apparently identical extent, pharmacological analyses of the PIE of ET isopeptides indicate that the PIEs of ET isopeptides are mediated by different subtypes. The PIE of ET-3 is more susceptible to the selective ETA receptor antagonists, BQ-123 and FR139317, than the PIE of ET-1: the main portion of the concentration-response curve for the PIE of ET-1 was not antagonized but rather enhanced by these selective ETA antagonists. Among ET receptor antagonists examined only TAK-044 could antagonize the PIE of ET-1. Data on pharmacological analysis by means of novel ET receptor antagonists imply that the pharmacological characteristics of ET receptor subtypes in the rabbit ventricular myocardium do not meet the conventional classification of ET receptor subtypes. The PIE of ET isopeptides is associated with the acceleration of phosphoinositide hydrolysis, which may be responsible for the increase in the amplitude of calcium transients and calcium sensitivity of contractile proteins.

ET receptors are likewise coupled to the inhibitory regulation of cardiac function: ET-1 inhibited the PIE (dog) and positive chronotropic effect (rabbit) of beta-adrenoceptor stimulation, which is mediated by pertussis toxin sensitive G protein. The inhibitory action of ET isopeptides was either associated with (rabbit) or not associated with (dog) decrease in cAMP level and was predominantly mediated by ETA (dog and rabbit) and partially by ETB (dog) receptors in the dog ventricular myocardium.